REMARKS

Reconsideration of the above-identified application in view of the amendment above the remarks below is respectfully requested.

No claims have been canceled or added in this paper. Claims 1, 6, 14 and 43 have been amended in this paper. Therefore, claims 1-31 and 35-44 are pending. Of these claims, claims 35-42 have been withdrawn as being directed at non-elected Groups. Therefore, claims 1-31 and 43-44 are under active consideration.

Claim 14 stands objected to for the following alleged informality:

> Claim 14 recites the limitation of "operatively linked to with unwanted side effects" in line 3 of the instant claim, and should be amended to read as –operatively linked to unwanted side effects--. Appropriate correction is required.

Applicants have amended claim 14 in the manner suggested by the Patent Office. Accordingly, the subject objection has been overcome and should be withdrawn.

Claims 1-31, 43 and 44 stand rejected under 35 U.S.C. 112, second paragraph, "as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." In support of the rejection, the Patent Office states the following:

> Claims 1 and 43 each recite the limitation "selecting the sites which are differentially methylated" in step (d) of either claim. The antecedent basis for this limitation in the instant claims are unclear as the previous method step (c) recites the limitation of "analyzing the cytosine methylation at chosen sites." As such, it is unclear from the instant claims if "the sites" recited in step (d) refer to the "chosen cites" as recited in step c) or if "the sites" of step (d) is intended to encompass the any differentially methylated site in the DNA of samples A and B. Claims 2-31 and 44 are also included under this rejection due to their dependence from either claim 1 or claim 43.

For the purpose of continuing examination, it has been construed that the limitation "the sites which are differentially methylated" in step (d) of either claims 1 and claim 43 is limited to the chosen sites of the DNA contained in samples A and B as recited in step (c) of said claims.

Claim 43 recites the limitation of "selecting sites which are differentially methylated between the DNA in biological samples A and B" in step (d) of the instant claim. However, the instant claim recites three separate preparative steps involving samples A and B (steps (a)-(c) of the instant claim) wherein the methylation of DNA in samples A and B is potentially altered. Step (a) involves obtaining a sample (sample A) exposed to at least one drug, chemical substance, and/or pharmaceutical that potentially may effect the methylation of DNA. Step (b) involves obtaining a second sample (sample B) which was not exposed to said at least one drug, chemical substance, and/or pharmaceutical and therefore does not have the same potential alteration to the methylation of DNA in the sample as in sample A. Step (c) is drawn to an analysis step wherein both samples A and B are chemically treated with at least one of bisulfite, hydrogen sulfite or disulfite, which will alter the methylation of DNA in both samples A and B. As such, the DNA of sample A has two methylation states, an initial state effected by at least one drug, chemical substance, and/or pharmaceutical and a second state wherein the DNA is altered by subsequent treatment with at least one of bisulfite, hydrogen sulfite or disulfite. Likewise, sample B has two methylation states, an initial native DNA methylation state from an untreated biological sample and a second state wherein the DNA of the sample is altered by treatment with at least one of bisulfite, hydrogen sulfite or disulfite. It is unclear from the instant claim which or in what combination these four sample methylation states are used to establish the differential methylation between samples A and B as recited in step (d). Claim 44 is also included under this rejection due to its dependence from claim 43.

For the purpose of continuing examination, it has been construed that step (d) of instant claim 43 drawn to selecting the sites which are differentially methylated between the DNA in biological samples A and B reads on selecting differentially methylated site

established between any combination of the above described methylation states of DNA from samples A and B.

In response to the above, Applicants have amended claims 1 and 43 to obviate the issues raised by the Patent Office. Accordingly, the subject rejection has been overcome and should be withdrawn.

Accordingly for at least the above reasons, the subject rejection should be withdrawn.

Claims 1-11, 13-21, 23-26, 28, 31, 43 and 44 stand rejected under 35 U.S.C. 102(e)(2) "as being anticipated by Laird et al. (P/N 6,311,393 B1)." In support of the rejection, the Patent Office restates the reasons from its January 12, 2005 Office Action and then states the following:

> The instant claims are drawn to methods for determining the biological effect and/or activity of at least one drug, chemical substance, and/or pharmaceutical composition comprising the steps of obtaining a biological sample A containing DNA, wherein said sample A was exposed to said at least one drug, chemical substance, and/or pharmaceutical composition, obtaining a biological sample B containing DNA, wherein said sample B was not exposed to said at least one drug, chemical substance, and/or pharmaceutical composition, subsequently analyzing the level of cytosine methylation at chosen sites of the DNA contained in samples A and B, selecting sites which are differentially methylated between the DNA in said samples to generate a knowledge base, and concluding the biological effect of said at least one drug, chemical substance, and/or pharmaceutical composition from said knowledge base.
>
> Laird et al. disclose a method for determining methylation patterns (biological effect or activity) in genomic DNA (containing genes) after being treated with sodium bisulfite (sample A)(chemical substance)(abstract), as stated in instant claims 1, 9, and 13. Laird et al. disclose methylation amounts in multiple samples are quantitatively determined based on reference to a control reaction (sample B)(col. 5, lines 61-64) which represents an unexposed sample and analyzing methylation levels in samples A and B, as stated in instant claims 1 and 43. Laird et al. disclose using probes and

primers to distinguish between methylated and unmethylated nucleic acid, amplifying the DNA, and detecting methylated DNA via fluorescence-based quantitative PCR (col. 5, lines 16-64) which represents selecting sites differentially methylated. Figures 7 and 8 display data that represent a knowledge base generated based on the conclusive effect of sodium bisulfite treatment, as recited in instant claims 1 and 43. The gene names (i.e. ESR1 or MyoD1) in Figures 7 and 8 represent additional information used for the conclusion data found in these figures (i.e. correlation between MLH1 gene expression, MSI status, and promoter methylation status of MLH1 in Figure 8, col. 24, lines 30-31), as stated in instant claim 24. The x-axes in the 2-graphs of represent at least two individual rows of analyses, as stated in instant claims 17 and 25. This data presentation also shows all or a part of the sites used for the conclusion, as stated in instant claim 23. Further conclusions are drawn by Laird et al. (col. 24, lines 48-67). Laird et al. disclose in higher order eukaryotic organisms, DNA is methylated only at cytosines located 5' to guanosine in the CpG dinucleotide (col. 1, lines 14-17) which represents cytosine methylation. Laird et al. disclose contacting a DNA sample from a patient with a modifying agent, bisulfite (col. 5, lines 19-20 and 31), as recited in claim 44. Laird et al. disclose various methods to identify altered methylation sites in cancer cells (col. 3, lines 3-5) and determining DNA methylation patterns at specific loci (col. 4, lines 12-15) which represents only one set of selected sites, as stated in instant claim 18. Laird et al. disclose selecting genes (col. 19, line 5) which represents a knowledge base of different classes, as stated in instant claim 19. Laird et al. disclose using PCR, sequencing, fluorescent labeling (col. 7, lines 26-65), as stated in instant claim 9. Laird et al. disclose using human colorectal adenocarcinoma (cancer) and normal nucosa (healthy) tissue samples (Figures 7 and 8; col. 22; lines 46-49), as stated in instant claims 4 and 5. Laird et al. disclose 25 match-paired normal and tumor samples with MLH1 expression level and MLH promoter methylation as well as MYOD1 control gene (Figure 8 and col. 8, line 64 to col. 9, line 12) which represent at least two methylation sites selected and analyzed in parallel, as stated in instant claims 11 and 21. Laird et al. disclose using parallel reactions with methylated, unmethylated, and control oligos of bisulfite-treated DNA samples (col. 18, lines 36-39). Laird et al. disclose analyzing methylation status of the ESR1 locus in DNA samples which is a gene that contains hypermethylatable CpG islands that undergo de novo methylation in human colorectal tissue

in all normal and tumor samples (col. 18, line 67 to col. 19, line 17 and col. 22, lines 29-30) which represents methylation sites are located in methylation relevant genes related with cancer, as stated in instant claim 14. Laird et al. disclose using PCR primers and probes used for sequences representing fully methylated and fully unmethylated DNA in several genes, including ESR1 (col. 19, lines 32-40), which represents analyzing all potential methylation sties of the DNA, as stated in instant claim 10. Laird et al. disclose isolating DNA via proteinase K digestion from sperm and HCT116 (human colorectal cell line), treated with sodium bisulfite, and then the DNA samples are analyzed by COBRA analysis or amplification process using fluorescence-based real-time quantitative PCR (col. 16, line 55 to col. 17, line 17), as stated in instant claims 6-8. Laird et al. disclose that altered DNA methylation pattern of cytosine residues is mutagenic (col. 2, lines 34-36) demonstrates that the colorectal samples mentioned above represent genes related with ulcerative colitis which is a type of colon disease, as stated in instant claim 15. In Example 4, Laird et al. disclose analyzing the methylation DNA samples from the same patient (col. 22, lines 29-32) which represents analyzing methylation sites that are personalized, as stated in instant claims 16 and 28. In Example 5, Laird et al. disclose using 25 patients with tumor and normal tissue samples surgically removed (dissected tissue immediately frozen)(col. 23, lines 28-37) which represents histologically, dissected biological material from healthy and diseased individuals in instant claims 2-4. Laird et al. disclose the use of paraffin embedded samples (col. 9, lines 42-46). Laird et al. disclose using the TaqMan, Lightcycler, Sunrise technologies, as well as ABI Prism 7700 Sequence Detection System (col. 14, lines 5-20) which represent selection at least partially performed automatically by an automate or computer device and conclusions performed by a computer system, as stated in instant claims 20, 26, and 31.

Later in the Office Action, the Patent Office states the following:

In regards to the rejection of claims as being anticipated by Laird et al., applicants argue that instant claim 1 requires (i) that biological sample A be exposed to the drug, chemical and/or pharmaceutical composition, (ii) that biological sample B not be exposed to the drug, chemical and/or pharmaceutical composition,

and (iii) that after said exposure or non-exposure, the level of cytosine methylation in biological samples A and B be analyzed.

In response, it is reiterated from the above rejection that Laird et al. discloses a method for determining cytosine methylation patterns in genomic DNA after being treated with sodium bisulfite, contacting a DNA sample from a patient with a modifying agent, (i.e. sodium bisulfate), and quantitatively determining DNA methylation patterns based on reference to a control reaction representing an unexposed biological sample. As such, applicant's argument fails to point out the patentable novelty of the claimed invention over the state of the art disclosed by the cited reference on which the rejection is based.

In regards to newly presented claims 43 and 44, applicants argue that Laird et al. does not teach or suggest obtaining a biological sample A that was exposed to at least one drug, chemical substance and/or pharmaceutical composition, obtaining a biological sample B that was not exposed to said at least one drug, chemical substance and/or pharmaceutical composition, and then analyzing the level of cytosine methylation at chosen sites of the DNA contained in the biological samples A and B, wherein said analyzing comprises chemically treating each of said biological samples A and B with at least one of bisulfite, hydrogen sulfite or disulfite.

In response, it is noted that Laird et al. discloses the collection and preparation of multiple biological samples from a patient, treating said samples with sodium bisulfate, and analyzing the methylation patterns of genomic DNA from said patient samples. In the instant case, the disclosed treatment of a patient sample with sodium bisulfate reads on the instantly claimed limitations of exposing a sample to at least one drug, chemical substance and/or pharmaceutical composition as well as treating said sample with at least one of bisulfite, hydrogen sulfite or disulfite. Further, the disclosed procedures also set forth obtaining an untreated biological sample (sample B) and subsequently treating said sample with at least one of bisulfite, hydrogen sulfite or disulfite.

Applicants respectfully traverse the subject rejection. As best understood by Applicants, the Patent Office is predicating the subject rejection on the position that the sodium bisulfite of Laird et al. constitutes the claimed "at least one drug, chemical substance and/or pharmaceutical composition." In response, Applicants note that the claims have been amended so that they are directed to "[a] method for the determining the biological effect and/or activity of at least one drug and/or pharmaceutical composition." As such, the claims no longer read on sodium bisulfite because sodium bisulfite is neither a drug nor a pharmaceutical composition. This is evident from the fact that sodium bisulfite has no known therapeutic use.

In conclusion, it is respectfully submitted that the present application is now in condition for allowance. Prompt and favorable action is earnestly solicited.

If there are any fees due in connection with the filing of this paper that are not accounted for, the Examiner is authorized to charge the fees to our Deposit Account No. 11-1755. If a fee is required for an extension of time under 37 C.F.R. 1.136 that is not accounted for already, such an extension of time is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,

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By: _____

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I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on November 6, 2006

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Edward M. Kriegsman